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in his laboratory at Pearl River, New York

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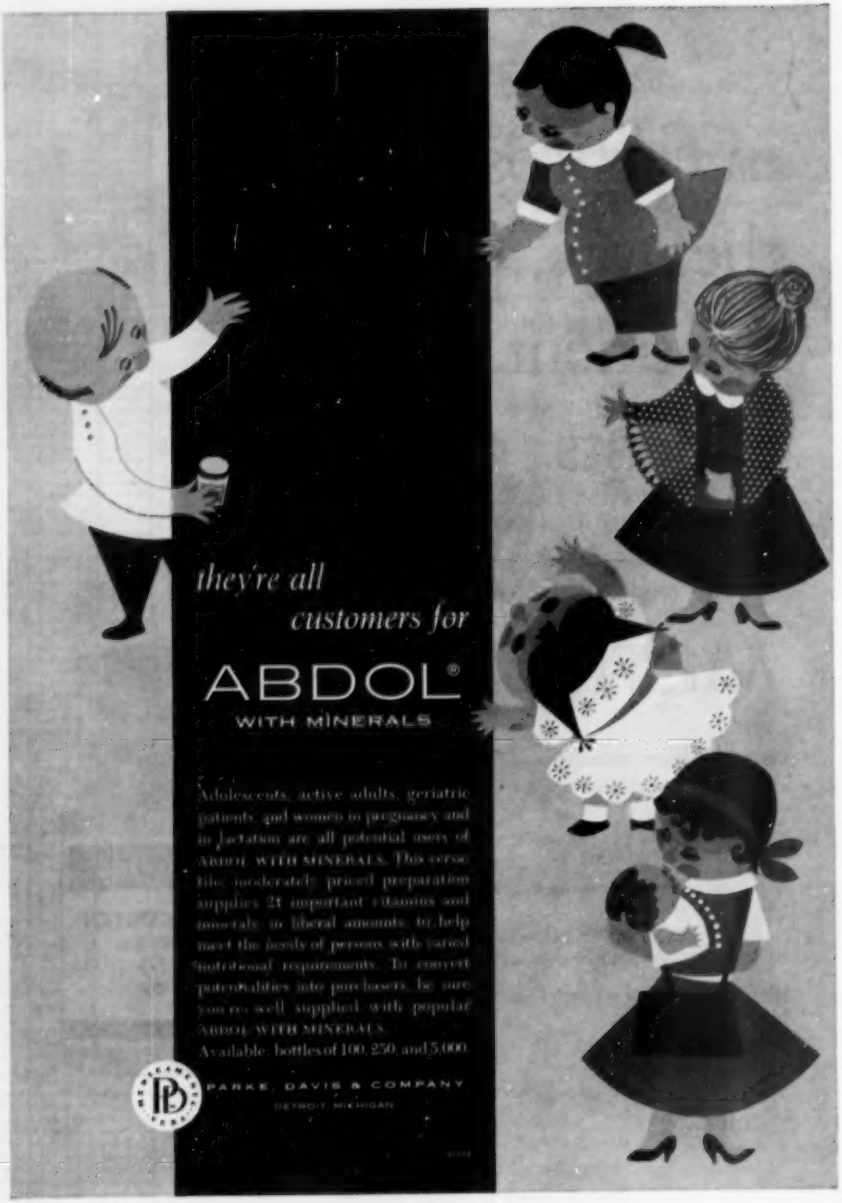
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EDITORIAL

THE LESSON AND EXAMPLE OF DR. DUGGAR'S LIFE

OUR cover this month shows the late Benjamin Minge Duggar working in the laboratory which he loved and from which came one of the greatest contributions of all time toward the alleviation of human suffering. Dr. Duggar died on September 10th at the age of eighty-four and, while he shall be missed, one cannot help believing that, in his last days, he must have reflected back on a life well-spent. Surely it was one of unusual length and one which brought to mankind far more than it is possible for most men to achieve.

We do not wish to comment on the importance of the discovery of the first broad spectrum antibiotic of the tetracycline group. This is known to every pharmacist, physician, and nurse throughout the world for it was, indeed, one of the greatest of this century. There are, however, certain aspects concerning Dr. Duggar's life which all of us should comprehend more fully since our failure to do this is costing us heavily and will continue to do so.

Dr. Duggar retired as Professor of Botany at one of our state universities in 1943 as was required there by law. At that time, most people—if not all—would have looked upon him as one whose contributions were over and who should spend the remainder of his days in quiet reflection of his past glories and accomplishments. This is the almost brutal attempt made today when most men retire, for society is quite cruel in inflicting on its older citizens a place in limbo from which escape is practically impossible. While it is a fine thing to make way for younger people who are eager to assume top positions and responsibilities, it is a serious mistake to do this unless, at the same time, the displacement of the older person is done in a way that his own interests and those of society at large are properly protected.

Nothing is more likely to shorten the oldster's life than a period of forced inactivity following a busy life to which he had become accustomed. Forced retirement under these circumstances is almost like a "kiss of death" and not all older people are fully conditioned to such

a radical change in their way of life. It is far better to have a gradual tapering off process, and it is surely impossible to fix an age at which all persons should retire. There are wide variations in the rate at which different individuals age, both physically and mentally. Some men are old at sixty and others are alert and able at eighty.

If the damage caused by forced retirement was suffered only by the individual in question, it would be tragic but not of such great social significance. The truth is that it is often quite harmful to society as a whole, and more attention must be paid this problem. Dr. Duggar's life in itself is ample proof of this since he discovered Aureomycin two years after his forced retirement. It just so happened that he did not let either law or society place him on the shelf, so to speak, where he would simply vegetate for his remaining years. Not only did he remain active, but he succeeded in making the greatest contribution of his life. It is not a coincidence that he managed to live to the age of eighty-four. Each of his days was an exciting experience and the will to live and the joy of living never ceased. Had he retired in the strict sense of the word in 1943, it is very doubtful that he would have lived to reach eighty.

Our American society is becoming more highly populated with older people each year and this trend will continue at an increasing rate. It is imperative that we utilize our older citizens for all the great contributions which they can make to our society and to our standard of living. Not that they should be kept at forced labor or that the retirement age should necessarily be raised but it should be made more an optional thing or, at least, special abilities used where it is evident that they exist, regardless of age.

We pay our last respects to Dr. Benjamin Duggar and urge everyone to reflect on the lesson which this great man's life has taught.

L. F. Tice

PROFESSIONAL STANDARDS IN DRUG MARKETING *

By Robert E. Abrams **

THIS assigned topic has caused me a great amount of consternation and I have spent two months trying to determine exactly what the scope of this presentation should be. I am still not certain that I have arrived at the proper conclusion but I trust that the thoughts presented are in line with the desires of the committee. Before we delve into this many faceted subject, we should agree on the meaning of the words used. The term profession is usually explained as a calling whose practitioners are extensively trained, who place the public welfare above financial acquisitions and who are self-regulating by abiding by some code of ethics laid down by its practitioners. What then is ethics? Over-simply, ethics is defined as the principles of right conduct. Behavior is ethical when it is right, unethical when it is wrong. However, who is to make the sharp delineation between right and wrong or is there such a sharp delineation?

How then does pharmacy measure up to this definition of a profession and can we attempt to apply "ethical" or "professional" concepts to pharmacy? We can if we decide on what "Pharmacy" we mean. For in pharmacy we have a most important segment known as the pharmaceutical manufacturing industry. Can we assign the professional label to it? I seriously doubt it and I do not mean this in any derogatory manner whatever but, in order for us to truly understand a situation, we must face facts realistically. Many, if not all, pharmaceutical manufacturers have their primary responsibility to their stockholders; they must show a marked financial return or they are no longer useful. This calls for an intense competitive effort which on many occasions has winked at if not truly violated what we personally believe to be truly ethical concepts. These actions are by no means confined to the pharmaceutical industry nor to pharmacy alone but seem to pervade our every dealing. The country and its people

* Presented at the Teachers' Seminar on Pharmacy Administration, Austin, Texas, July 1956.

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seem to be placing too great an emphasis on the acquisition of wealth come what may and, wh n the choice is between money and ethics, ethics often runs a somewhat poor second.

The likely question then is "What about the practicing pharmacist"? Does he meet the definition of a profession? In many cases he does. His efforts in providing true community service have stamped him as one of the most wholesome influences in the community. However, there is one phase of our definition which he has failed to fulfill; namely, he has not exhibited the degree of self-regulation which a profession must exercise. Now it is true these statements do not apply to all pharmacists but frankly, although their percentage is relatively small, there are still enough "rotten apples" in the barrel to make the price of the barrel much less than what it should be.

With respect to the teaching of Pharmacy Administration, I strongly and sincerely believe that the subject of Ethical Concepts in Drug Marketing should be presented to the student, not in a hurried manner but in a most frank and comprehensive way. We are not fulfilling our obligation if we do not provide the student of pharmacy with a true insight into the problems of pharmaceutical marketing and thus possibly better equip him to handle situations which he may encounter when he goes out into practice. I know there are some who believe that sin should never be discussed but, if virtue and sin are not presented, how is one to make a decision? Too many educators confine themselves to discussions of pure scientific facts and ignore the rigors of human nature. We are responsible for graduating more than just scientific robots; we must see that our students are cognizant of the true facts of life and are capable of deciding what is good for the profession and what is bad for it. The problem of ethics in all its ramifications should be discussed realistically and a frank evaluation is the only approach.

When I initially started to write this paper, it was my intention to take a product and trace it from beginning to end covering all the instances where ethics comes into play but after I reached about the first six of sixty stages I had twelve pages of manuscript and realized that, if this were to continue, I would have to write a book. Therefore, it is my intention to present only the subjects or problems in outline form without detailed discussion. These subjects are ones which I believe to be important enough to be discussed in a course or series of lectures on this topic. Since most pharmaceutical products travel

the route of manufacturer, wholesaler and retailer, for ease of presentation, let us divide our proposed subject matter into these three categories.

I. Manufacturing

A—*Pre-Introduction of a New Product*

1. Does it really fill a need or is it another duplicate?
2. Is it superior to other products on the market?

B—*Submission of N. D. A. Data*

1. Has all data been submitted both positive and negative?
2. Have the side-effects in the number of cases indicated more work on the drug?

C—*Introductory Literature*

1. Has enough attention been called to side-effects and in the initial brochure are they printed in large enough type?
2. Does all literature bear the precautionary statements?
3. Has the pharmacist received the initial information on the use and dangers of the product?

D—*Shipments and Sales*

1. Sales to pharmacies direct or through wholesalers.
2. Should the manufacturer sell direct to the physician?
3. Sales to physician-owned pharmacies, clinics and hospitals.

E—*Pricing of the Product*

1. Is it priced within reason with respect to its cost or is the "all that the traffic can bear" principle applied?
2. Should the representatives, salesman or detail man inform the physician of the price of the medication?
3. Is it priced equally with certain trade discounts?
4. If it can be sold O-T-C and is fair-traded, is the margin offered adequate?

F—*Over-the-Counter Products*

1. If the product is considered safe for over-the-counter sale, should it be sold to super-markets as well as pharmacies?
2. Is the advertising honest or does it hold out claims for effectiveness which cannot possibly be fulfilled?

G—*Returned Goods Policy*

1. In return for rapid stocking of a pharmaceutical product, does the manufacturer provide a reasonable return goods policy?
2. Should credit given for pharmaceuticals be in the form of cash or merchandise and by whom should the credit be issued?

H—*Intraprofessional Relations*

1. Is every effort made to understand the thinking of the wholesaler and retailer?
2. Is sufficient support given to the Colleges of Pharmacy?

II. The Wholesaler

A—*Sale of Products*

1. Is merchandise fresh and in date?
2. Are legend drugs restricted to only licensed outlets?
3. Is the stock relatively complete and comprehensive?

B—*Pricing of Products*

1. Are all contracts honored?
2. Are additional services and prices offered for high volume consumers?
3. Are all prices accurate and correct?

C—*Intraprofessional Relations*

1. Is every effort made to assist pharmacists in worthwhile services and projects?
2. Is proper support given to the Colleges of Pharmacy?

III. The Pharmacist

A—*Filling of Prescriptions*

1. Substitution.
2. Refilling of Prescriptions.
3. Should legend drugs be sold without prescription?
4. Are the highest quality products offered?

B—*Pricing of Prescriptions*

1. Fair to consumer.
2. Fair to pharmacist and other pharmacists.

C—*New Products*

1. Availability of New Products.
2. New Product information.

D—*Information*

1. Providing up-to-date information to the medical profession on new and old products, particularly their side effects.
2. Providing information to the public on all matters of public health.
3. Is it ethical to encourage the use of generic names?

E—*The Pharmacy*

1. Appearance—Is it professional looking?
2. Are its personnel qualified?

F—*Sales of Over-the-Counter Items*

1. Is proper supervision exercised?
2. Do customers receive what they ask for?
3. Are trading stamps ethical?

G—*Community Service*

1. Active participation in community projects.
2. Active participation in professional societies and projects.
3. Co-operation with allied professional groups.

H—*Continued Education*

1. Attendance at lectures, seminars and conventions.
2. Maintenance of adequate library.
3. Continuous efforts to keep informed.

I—*Physician Relations*

1. Sales to physicians.
2. Presents to physicians.
3. Prescription blanks.
4. Direct lines.
5. Direction by physicians of patients to a particular pharmacy.

J—*Professional Advertising*

1. Disparaging statements.
2. Improper offers or implications.

K—*Intraprofessional Relations*

1. Co-operation with fellow pharmacists.
2. Support and active participation at Colleges of Pharmacy.

L—*Hospital Pharmacy*

1. The Formulary system, is it fair?
2. The filling of out-patient prescriptions.
3. The pricing of prescriptions.

M—*Welfare—Voluntary and Other Health Plans*

1. Does it allow free selection of pharmacy and pharmaceuticals?
2. Does it provide adequate service and care?

I realize there are many other topics that might be included in any of these three categories. It is impossible however to mention them all here. The discussions on some of the topics mentioned were very brief but, if we were to go into detail on each, it might take the remainder of the summer vacation. These subjects, we do believe are important and deserve frank and open discussion somewhere in the curriculum for, if ignorance of them is not corrected, then a possible solution to these problems may never be forthcoming.

NEW ANTIBIOTICS IN THE FIGHT AGAINST RESISTANT STAPHYLOCOCCI *

ONE of the most serious problems in the current practice of medicine is that of antibiotic-resistant staphylococcic infections. Whereas staphylococci were once almost always susceptible to penicillin therapy, today a high per cent of strains are resistant to penicillin and many other antibiotics as well. It seems that our continuing fight against these bacteria has made them stronger and more virulent rather than weaker. This is particularly true in some hospitals where patients only too often acquire a staphylococcic infection resisting all known forms of therapy. The infection may be in the form of a septicemia or a staphylococcal enterocolitis. In the latter case, some authorities consider this to be a complication of broad spectrum antibiotic therapy. The antibiotic suppresses the normal intestinal flora but is of no effect on staphylococci which then multiply rapidly.

Development of Resistance

Even though an antibiotic is initially effective against a given organism, its continued and extensive use is likely to result in the emergence of resistant strains. The reason usually given for this is that, while most individual organisms are killed, an occasional mutant emerges that is not affected. Such a mutant is able to withstand the drug by the adoption of some alternate metabolic pathway not blocked by the antibiotic in question. Staphylococci seem unusually inclined to become resistant as compared with other organisms, although it is not restricted to them alone. Once resistance has developed, it is retained by successive generations of the bacteria. Patients infected with such organisms cannot be treated with the antibiotic successfully and the results are serious indeed unless some other antibiotic having an effect is known and available.

Importance of New Antibiotics

In recent years, there has been an intensive and continuous search for new antibiotics. This has taken place not only because of the com-

* From the Department of Pharmacy, Philadelphia College of Pharmacy and Science.

mercial importance of such new discoveries but also because it was realized that, without them, the medical profession might be confronted with mutant strains of certain bacteria against which all forms of treatment would be to no avail. Some writers have predicted that this will eventually happen but, so far, intensive pharmaceutical research has kept the physician prepared against such emergencies.

In some countries, the government has banned the widespread use of certain antibiotics solely for the purpose of reserving them for infections not responding to any other form of therapy. This has been done since any antibiotic, if it is used extensively, will in time lose its effectiveness against some organisms; notably, staphylococci. This is true even though the antibiotic may have been very effective when first introduced in medicine.

Erythromycin

This antibiotic was made available only a few years ago (1952) and its most important property was its effectiveness against organisms that had acquired resistance to penicillin and certain of the broad spectrum antibiotics. It is still useful for this purpose but, in those areas where it has been widely used, it is showing signs of losing its activity against staphylococci. Here, it must be emphasized that this is not a fault peculiar to erythromycin. There is every reason to believe that eventually the same thing will happen even with the most recently discovered antibiotics. Some medical authorities even have gone so far as to recommend the complete withdrawal of certain antibiotics from medical use for a prolonged period. This would make possible restoring them to their original effectiveness as mutant strains of bacteria gradually were replaced with those having more normal metabolic pathways. Such a phenomenon was actually observed with chloramphenicol. It fell almost into disuse for a period of time when it was given an unwarranted reputation of causing blood dyscrasias. When these fears were proved without basis and it was again adopted widely, it was found to be as effective as when it was first introduced.

Since any given antibiotic may be expected to lose its effect in time, the search for new ones is of vital importance. Antibiotics are very complex substances and there is not much likelihood that they can be altered chemically to restore their activity. No-one knows how many antibiotics are as yet undiscovered but the present effort to find them is stupendous.

Novobiocin

This is one of the most recently discovered antibiotics showing outstanding anti-staphylococcal activity. It has, in addition, some other important uses.

Three antibiotic substances isolated independently in three different pharmaceutical laboratories were finally shown by Welch and Wright of the U. S. Food and Drug Administration to be the same substance. This was done using ultra-violet and infra-red absorption curves and crystallographic data. The three substances were Cathomycin (Merck Sharp & Dohme) isolated from *Streptomyces spheroides*, Streptonivicin also known as Albamycin (Upjohn) isolated from *Streptomyces niveus*, and Cardelmycin (Pfizer). The generic name for this new antibiotic is Novobiocin. The antibiotic Albomycin, recently announced by the Soviet Union, was isolated from *Actinomyces subtropicus*. It is not identical with the Upjohn product Albamycin and should not be confused with it.

Novobiocin is a yellowish-white crystalline powder. Its chemical structure is not yet known but it is a dibasic acid with a pK at 3.8 and 9.4. It is insoluble in water but its monosodium salt is very soluble. The pH of a 1 per cent solution of the monosodium novobiocin is 7.5-8.0. Acidification causes the precipitation of the acid form. A hemi-calcium salt (half neutralized) is also available. Novobiocin is quite stable even in the presence of water both as the acid form in aqueous suspension and in solution as the monosodium salt. Novobiocin in 0.1*N* sodium hydroxide solution shows a strong absorption band at 307 mμ and has an extinction coefficient of 600 (A 1%/1 cm.).

It can be assayed microbiologically in plasma, serum, or urine and a colorimetric assay has been reported using Gibbs reagent (N,2,6-trichloro-p-quinoneimine).

Bacterial Spectrum

Novobiocin appears to be effective against most strains of staphylococci, streptococci, pneumococci, Neisseria, Corynebacteria, Pasturella, Erysipelothrix, and Proteus. It is not effective against *Aerobacter, B. pyocyaneus, Pseudomonas aeruginosa, Escherichia coli, Salmonella typhosa,* and *Shigella dysenteriae*. It is particularly efficient against strains of staphylococci and streptococci which are resistant to penicillin and other antibiotics.

Novobiocin is reduced in its antibacterial activity by the presence of blood serum but it is not destroyed by it. It appears to be bound by serum albumin but reversibly so since it can be extracted from it intact.

In vivo, cross-resistance studies using *Staphylococcus aureus* have not shown any significant cross-resistance between novobiocin and penicillin, streptomycin, oxytetracycline, chlortetracycline, chloramphenicol, or erythromycin.

Absorption and Excretion

While novobiocin can be given parenterally, it is rapidly absorbed from the gastro-intestinal tract and produces high and prolonged blood levels. A single oral dose of 500 mg. will result in blood levels of 25-50 μg/ml. lasting up to 6 hours. If a dose is given every 6 hours, blood levels are maintained fairly uniformly during the treatment period. Little, if any, of the drug gets into the spinal fluid and the level found in the urine is very low. It is found in pleural and ascitic fluid.

There is some evidence that the drug is excreted by the liver and then reabsorbed, thus giving it a prolonged effect.

A yellow metabolite of novobiocin colors the plasma and may make the sclera of the patient appear as if jaundiced.

Side Effects

Novobiocin sometimes causes slight gastric distress and nausea. A dermatitis has also occurred in a few patients; this is believed an allergic response. More recent experience with purer material has given a much lower incidence of dermatitis and urticaria. It is also claimed by some clinicians to have caused some liver disturbance, but the yellow metabolite of novobiocin complicates the determination of the icterus index and simulates jaundice. No gross liver damage has yet been observed. There is some possibility of blood dyscrasia since one patient on novobiocin therapy developed leukopenia. Retreatment of this same patient at a later date did not produce any significant effect.

Dosage

The usual dose for adults is an initial dose of 1 Gm. followed by 250 mg. four times daily, taken on an empty stomach to facilitate

absorption. Higher doses may be needed in severe or resistant infections. Dosage may be continued if necessary for two weeks or more.

A sterile solution of the monosodium salt can be given intravenously or intramuscularly, but the latter route is somewhat painful.

A pediatric suspension of free novobiocin 125 mg./teaspoonful has also given good results in children.

There is good evidence that combined therapy with novobiocin and penicillin is desirable. This broadens the antibacterial spectrum and tends to reduce the chance of resistant strains emerging.

Other Antibiotics

While novobiocin is the latest antibiotic released having marked activity against resistant cocci, others are under clinical trial. Some of these look very promising. Among these are P. A. 105 (Pfizer) isolated from a strain of *Streptomyces antibioticus*. This substance is also known as Oleandomycin and is marketed as Matromycin by Pfizer. In some respects, it seems superior to novobiocin and, in one study, not a single strain of staphylococci was found resistant to both P. A. 105 and novobiocin. The spectrum of P. A. 105 is quite similar to that of erythromycin and novobiocin.

Still other antibiotics in this category and under clinical investigation are Vancomycin (Lilly) and E129 (Glaxo). One can only speculate whether man's ingenuity and effort in finding new antibiotics will eventually win the long battle against the cocci. These hardy organisms have troubled and sickened man since the dawn of creation and still resist some of our best therapeutic efforts.

IN VIVO EXPERIMENTS WITH CARCINOGENS. X.

By John R. Sampey *

THE extent of the current interest in agents inducing cancer in man and laboratory animals is indicated by the 1740 articles surveyed by the author in this and earlier studies (191). The present paper reflects continued interest in tobacco, tissue and cell extracts, hydrocarbons, radioactive isotopes, organic nitrogen compounds and hormones as carcinogens.

I. Inorganic Chemicals

Radioisotopes. Several clinical investigations have been made of patients having leukemia, following prolonged use of radioiodine (11, 41, 204, 205, 206). Injury to the thyroid gland by large doses of I^{131} has been reported (133, 143), but Field, et al. (63), noted no neoplastic changes in rats given 273 mc. of the isotope in single injections. King, et al. (115), reported cancer of the larynx in a patient after thyroid-ablating dose of 51 mc. of radioiodine, and Edelman (54) employed I^{131} or Na^{24} for thyroidectomy in man. Silberberg (211) correlated joint lesions in mice with hypophyseal tumors induced by radioiodine.

Pu^{239} and U^{238} induced bone tumors in mice (64, 135). Intragastric balloons containing P^{32} produced squamous cell carcinoma in mice (153). Y^{90} caused skin lesions in a patient (170). A high incidence of breast tumors was observed in rats after doses of At^{211} (89). Co^{60} produced less skin reaction in patients than X-rays (18). Small doses of Au^{198} caused hepatomas in mice and large doses resulted in death from hepatic degeneration (234).

Thorotrast. Two reports have been made of carcinoma in patients receiving thorotrast injections years before (95, 188).

Metals. Thorium injections induced sarcoma in rabbits (109). Silver foil, tantalum, stainless steel and vitallium caused sarcomas in rats (168), and zinc salts caused lesions in the testicles of dogs (178). Stomach lesions were produced in mice by gallium citrate (161), and

* Furman University, Greenville, South Carolina.

DMBA carcinogenesis was increased by silver nitrate (210). No lung tumors developed in rats fed selenium for 16 months (118).

II. Hydrocarbons

Methylcholanthrene. MC continues as the leading hydrocarbon in the induction of a broad spectrum of neoplastic growths (17, 75, 98, 99, 100, 107, 117, 131, 132, 151, 161, 167, 186, 187, 207, 208, 221).

Benzpyrene. Benzpyrene produced skin neoplasms in animals (94, 174, 175, 176, 239), and tumors in the renal pelvis (72), and in transplanted nodules in mice (40).

Anthracenes. Sarcomas were induced in rodents by subcutaneous injections of anthracene (47, 195). Benzanthracene caused neoplasms in rodents (48, 94), and feeding dibenzanthracene resulted in carcinoma of the forestomach (221). Dimethylbenzanthracene, DMBA, produced a number of neoplasms in animals (35, 42, 77, 94, 190, 210, 239).

Other Hydrocarbons. Inhalation of paraffin vapors induced bronchial lesions in guinea pigs (30), and mineral oil caused hyperplasia in laboratory animals (17). Methoxy derivatives of polycyclic hydrocarbons caused sarcomata at the site of injections (199). Graffi (76) studied the mechanism of the action of carcinogenic hydrocarbons in mice. Eight of nine fractions of hydrogenated coal oils induced neoplasms in rats, mice and rabbits (102).

III. Organic Nitrogen Compounds

Aminofluorenes. Acetylaminofluorene, AAF, induced liver damage in experimental animals (4, 123, 156, 173, 194, 212), and it also resulted in stomach lesions (184) and atypical proliferation of lymphatic tissue (213). Diacetylaminofluorene caused liver lesions in rats (157).

Urethan. Urethan has been employed to induce lung tumors (2, 65, 105, 185, 209), and skin papillomas (8) in laboratory animals.

Amino Acids. Liver injury resulted from feeding ethionine (61, 62, 121). Deficiency of sulfur-containing amino acids in the diet caused hepatic injury (86). DON caused damage to the intestines of animals (220).

Azo Compounds. Several studies have been made on liver damage by azo dyes (43, 71, 93, 218).

Aromatic Amines. Several aminobiphenyls induced bladder tumors in dogs (38), and tumors in breasts of rats (150). Xenylamine developed bladder tumors in workers exposed for years to this dye intermediate (148), and alpha-and beta-naphthylamines and benzidine also caused bladder tumors in workers (21). Auramine and magenta were two other carcinogenic dyes (22).

Thiouracil. This compound induced a number of neoplasms in rodents (33, 142).

Nitrogen Mustard. Nitrogen mustard injections caused hepatic tumors in rats and rabbits (235). A combination of HN2 and AAF resulted in atypical proliferation of lymphatic tissue in rats (213).

IV. Hormones

Estrogens. Jensen and Ostergaard (108) reported 16 patients with cancer of the corpus uteri had taken extrogen treatments for 2 to 15 years, but Maurer (147) believes women have adequate counter-regulation for excessive estrogens. Winter (238) found no histological evidence to confirm a relationship of uterine carcinoma in a patient on estrogen therapy for a long time. Estradiol caused pituitary tumors in rats (207), and follicular hormones with croton oil induced an ovarian tumor (172). Ovaries grafted into the spleens of gonadectomized mice produced ovarian neoplasms (80, 84). Adenoma were produced in mice by ovarian and hypophysis transplants (134).

Androgens. Pellets of testosterone in hamsters induced 7 different types of tumors (116).

Cortisone. Cortisone increased the incidence of MC epidermal tumors in mice (98, 99) and it hastened the growth of Ehrlich adenocarcinoma in mice (39), and in rabbit eyes (66).

Thymectomy. Many lymphomas developed in thymectomized, irradiated mice bearing non-irradiated thymic grafts (20, 112, 113, 114).

ACTH. Combinations of ACTH and AAF induced preneoplastic changes in the livers of rats, but ACTH alone did not (212).

V. Miscellaneous

Smoking. The search for carcinogens in tobacco proceeds at an accelerated pace (6, 7, 23, 24, 27, 28, 29, 32, 45, 49, 56, 57, 58, 67,

69, 70, 73, 79, 96, 119, 124, 125, 126, 136, 139, 141, 154, 155, 159, 164, 165, 179, 180, 189, 192, 214, 215, 216, 223, 224, 225, 228, 237, 242, 243, 244).

Tissues and Extracts. A number of human cancers have been induced in experimental animals by tissue transplants and extracts (3, 90, 97, 111, 127, 166, 203, 229, 241). Leukemia has been transplanted in other experimental animals by similar techniques (52, 78, 81, 82, 129, 146, 169, 171, 202, 222, 240). Other neoplasms transplanted similarly include Yoshida sarcoma (196, 197), ascites tumor (1, 227), S-37 and S-180 (236), epithelial lesions (149), salivary gland carcinoma (55), adenocarcinoma (144). Koprowsky (122) induced tumors by injection of tumor cells in embryonic mice.

Occupational. Industry continues to pursue its search for occupational and environmental cancers (5, 12, 13, 16, 31, 44, 46, 59, 68, 101, 103, 145, 181, 198, 217, 231, 233).

Viruses. Viral concepts of inoculation have been studied in Hodgkin's disease (14), leukemia (50, 51, 52, 53, 162), lymphomas (19), rous sarcoma (137, 138), and HST virus (88). Urethan and influenza virus induced lung tumors in mice (105).

Diet. Davies (36) thinks the high incidence of live carcinoma in African tribes is due to diet deficiency in animal protein and fat. Metastases to the liver and lung have been noted in rats fed DAB and a low protein diet (160). An 80% incidence of breast tumors was noted with rats fed a fat rich diet (37). Overheated fats and a fat rich diet caused gastric lesions in rats (107). Overfeeding did not accelerate the growth of Walker C-256 (106). Low choline diet induced liver cysts in rats (92). Truhaut (232) warned of the danger of cancer from foreign substances in foods.

Cholesterol. Impure cholesterol caused more tumors in mice than the pure product (10).

Diabetes. Diabetes is 8 times as great in women with breast cancer as in the general population (182).

Croton Oil. Croton oil enhanced MC carcinogenesis (117), and it was the promoting agent in urethan skin tumors (8). Fractions of croton oil were tumor inducing (34, 85).

Plastics. Polyethylene plastic implants caused giant cells (9), and polyamides caused carcinoma and sarcoma in mice (200). Six

different polyvinyl pyrrolinodes caused sarcomas in rats (104). Methyl metacrylate implants produced sarcomas in mice (128).

Radiation. Genetic and carcinogenic effects of atomic radiations are receiving increased attention (25, 26, 152). Lung tumors were induced in mice by radium emination (110).

Wounds. Cancer has come as a sequel to war wounds (74), thermal burns (130, 177), and from a wood splinter (60).

Talcum. Talcum glove powder caused granulomas 10 years after an operation (83).

Alkaloid. Senecio Longilobus induced liver necrosis and ascites in rats (91).

Organic Halides. Bromobenzene induced liver damage in rats (120), and carbon tetrachloride caused liver necrosis in rodents (140, 226).

Ammonium Chloride. Nemeth, et al. (163), reported precancerous changes in the stomach of rats given this salt, which resembled those caused by benzpyrene, DAB, etc.

Quinones. Lymphomas were induced in rats by quinones from beetles (219).

Soils. Tromp and Diehl (230) held that there is a positive relationship between soils and cancer in Holland.

Phenols. Pipilomas in 60 to 70% of mice treated with phenols (15).

Sunlight. Fairskinned people are subject to sunlight carcinogenesis (87).

Anemia. Mosbeck (158) reported significantly higher incidence of cancer of the stomach in relatives of 234 patients with pernicious anemia than in controls, and Shell, et al. (193), studied 94 cases of the 2 diseases associated at Mayo Clinic from 1906 to 1950.

Personality Factors. The relation of personality factors to the incidence of cancer is under investigation (183, 201).

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SELECTED ABSTRACTS

The Making of Press-Coated and Multi-Layer Tablets. Tsevdos, T. J. *Drug and Cosm. Ind. 78:*38 (1956). The author briefly discussed the historical background of press-coated tablets (tablet-within-a-tablet) and multi-layer tablets, their application and the characteristics of the machines required to make them.

Typical applications in which press-coated tablets can be seen to be advantageous as compared with pan coating are: where water cannot be used because of its effect upon the tablet ingredient, the combination of incompatible ingredients by placing one in the core and the other in the press coating, the application of an enteric or delayed action coating as the press coat with accurate control of the thickness, and better product identification by the embossing or engraving of a product trade-mark on the tablet coating.

Two types of tablet presses are available for press coating. With one type, two presses are coupled together. One makes the core and then transfers the core to the second machine which presses on the coating. The other type of machine takes previously compressed cores and presses a coating around them. The latter type is more flexible since the cores may be made on any ordinary tablet press, controls run on the cores, and then the coating compressed on with the special press-coater. With this machine, a small amount of granulation is fed into the die, the core is centered on top of this granulation, more granulation is fed into the die on top and around the core, and the punch presses the coating granulation around the core. Any tablet that does not have a core in it is automatically discarded. Such a press-coating machine must be able to accurately center the core, it must provide accurate control of the thickness of the press coating on all sides at various operating pressures, it must be easy to operate, it must effectively reject finished tablets not having a core, it must be able to deliver 500 or more tablets a minute, and it must be adaptable for standard tablet compression if desired.

The multi-layer tablets are primarily used to separate ingredients which are incompatible. With modern multi-layer tablet presses, one ingredient may be compressed in the first layer of the tablet, additional granulation containing another ingredient is placed in the die

on top of the first compressed layer and the whole is then pressed. Two- or three-layer tablets can thus be made. Each layer can be accurately controlled.

The author concluded that these two new methods of tablet pressing hold many and varied possibilities for application in the pharmaceutical industry.

The Treatment of Acute Gouty Arthritis With Oral Phenylbutazone. Wilson, G. M., Jr., Huffman, E. R., and Smyth, C. J. *Am. J. Med. 21:232* (1956). Phenylbutazone was given orally in the treatment of 60 acute attacks of gout. Four different dosage schedules were employed in an attempt to evaluate the relationship of dosage to the clinical results obtained. The four schedules were: 100 mg. every four hours (4-6 doses a day), 200 mg. every four hours (4-6 doses a day), and 400 or 800 mg. as a single dose. The period of drug administration ranged from 1 to 5 days.

The rapidity of pain relief varied with the dosage. With the dosage of 100 to 200 mg. every 4 hours, in only 18 of 39 attacks was pain relief obtained within 8 hours. However, with the 400 and 800 mg. dosage, pain relief was obtained within 4 hours in 16 of 19 attacks. Pain was controlled in 56 of 58 attacks within 24 hours. Within 72 hours, joint inflammation was resolved in 47 of 51 attacks. Blood level studies showed that the attainment of a blood level which was effective in producing the relief of pain coincided with the clinical subjective relief from pain and averaged 3.09 mg. per cent.

The authors characterized the effects of oral phenylbutazone on acute attacks of gouty arthritis as dramatic. There was a rapid initial relief from pain followed by a gradual resolution of the signs of joint inflammation. In this type of arthritis, the response to phenylbutazone therapy was so dramatic that the authors suggested that this property might be useful as a diagnostic means to distinguish acute gouty arthritis from other forms of arthritis.

The authors recommended the following dosage schedule: a large initial dose of 400 to 800 mg., followed by the intermittent administration of 100 to 200 mg. 4 times a day for 3 days, or until the attack resolves. It was found that, although the large initial dose brought rapid pain relief, the effect was not always sustained and further supplemental therapy was necessary to maintain improvement and resolve the attack.

The Use of the Topical Antipruritic Agent Dyclonine Hydrochloride. Morginson, W. J., Rich, C., Eskelson, Y. D., Kirkman, L. W., Utterback, M., Burton, A. M., and Coletti, J. M. *Postgrad. Med. 19*:605 (1956). Dyclonine hydrochloride (4-n-butoxy-beta-piperidinopropiophenone hydrochloride), a new chemical agent having an antipruritic action, was evaluated in various dermatologic conditions on 222 patients. The compound was administered by topical application in a nonionic vanishing cream base having the formula:

Dyclonine hydrochloride	1.0 per cent
Stearic acid	18.0 per cent
Polyethylene glycol 1000 monostearate	8.0 per cent
Polyethylene glycol 400 monostearate	5.0 per cent
Beeswax (white)	2.0 per cent
Hydrous chlorobutanol	0.3 per cent
Distilled water q.s. ad	100.0 per cent

The results from this topical treatment were based upon subjective evaluation of relief from pruritus. On this basis, 57 per cent of the patients reported effective control of the itching. While the authors admitted that this was not an exceptionally high percentage, they indicated that the patients obtaining relief were highly satisfied with the preparation in comparison with many previously employed remedies. In paired studies on 33 patients, the base alone gave no relief from itching while the medicated cream did provide relief.

The greatest effectiveness was obtained in those cases where there were inflamed, excoriated and broken surfaces. There was apparently no effect on the dermatoses except for relief from pruritus. There was no observed effect on inflammation, epithelization or the flora of bacteria or fungi. In 8 cases of the 222, there were adverse reactions in the form of an increased severity in objective dermatitis and subjective discomfort during the course of treatment.

The Treatment of Megaloblastic Anemia of Pregnancy and the Puerperium With Vitamin B12. Adams, E. B. *Brit. Med. J.* No. 4998:398 (1956). Early reports on the use of vitamin B_{12} in the treatment of megaloblastic anemia of pregnancy and the puerperium indicated that the results were not satisfactory. However, interest in larger doses has increased as a result of recent studies.

Consequently, the author studied the use of massive doses of vitamin B_{12} in 10 patients with confirmed diagnosis of megaloblastic anemia. The doses employed were 100 μg., given in one intramuscular injection daily from 1 to 14 times.

Before treatment was begun, the patients were observed for 4 to 7 days. During this control period and the trial period which followed, progress was evaluated from daily reticulocyte counts, by hemoglobin levels, and by the volume of packed cells (P. C. V.).

The response was satisfactory in all seven patients treated after delivery. There appeared to be no advantage to giving doses greater than 100 μg. of the vitamin. Folic acid was given in a dose of 10 mg. three times a day to two patients after treatment with vitamin B_{12}. There was no additional improvement when the folic acid was given. The results of treatment were poor in the three patients treated before delivery. However, in all three patients there was a protein malnutrition which may have been a factor in the poor response from the administration of vitamin B_{12}.

The author concluded that, because of differences in the appearance of the bone marrow and in response to treatment, it seems likely that there are several varieties of megaloblastic anemia associated with pregnancy.

The Effect of Benactyzine in Psychoneurosis. Hopkins, S. J. *Pharm. J. 176:*333 (1956). Benactyzine (diethylaminoethyl ester of benzilic acid) is an anti-cholinergic drug that has been found to have a marked effect in the relief from tension. Its activity is closely related to its structure for small variations may result in a loss of activity. The molecule apparently functions as a whole, for neither the benzilic acid nor the ester fragments show any activity.

The action of benactyzine differs from other drugs used for the relief from tensions in psychiatry. It appears to have the effect of raising the threshold for external stimuli. This causes an individual in a state of tension who receives benactyzine to be able to view his problems in a more detached way. He is no longer overwhelmed by the fears associated with these problems. The drug acts as a sort of insulator. The drug also appears to block some of the pathways of the normal spontaneous association of ideas. After the administration of the drug, a condition of absentmindedness or thought blocking may be experienced. There is no sense of hallucination, since the intellect

remains clear, but powers of concentration are reduced and an increased forgetfulness may be observed.

The effect of benactyzine requires time to develop. Continuous treatment for one to two weeks is usually necessary before the action of the drug can be evaluated. The usual dose is 1 to 2 mg. three or four times a day. Frequent administration is necessary because of the rapid elimination of it from the body. Increased dosage may result in the development of side effects. Those most frequently noted are: dryness of the mouth, visual disturbances due to difficulties in accommodation, and nausea.

Polyvinylpyrrolidone Iodine as a Topical Germicidal Agent. Bogash, R. C. *Bull. Am. Soc. Hosp. Pharm. 13:226* (1956). Polyvinylpyrrolidone forms a complex with iodine which is considered to be an iodophor. The complex thus formed minimized most of the difficulties previously associated with iodine. The oral toxicity of the iodine complex was appreciably less than that of iodine. It was nonirritating in eye irritation studies on guinea pigs and nonsensitizing in skin tests on 200 human subjects. Upon drying, PVP Iodine solutions form films which may be left in place as a protective covering or they may be removed with water. It may be washed from linens and other natural fabrics with water without leaving a stain. The compound is both soluble and stable in water and yet retains the chemical and germicidal properties of iodine.

PVP Iodine was used in the treatment of a variety of infections encountered in the practice of otolaryngology, orthopedics, orthopedic surgery, obstetrics and gynecology, oral surgery, pediatrics, general surgery, and dermatology. The compound was applied in the form of solutions ranging in strength from 0.02 to 1.0 per cent available iodine and in ointments of 1.0 percent available iodine on a total of 5,900 patients. Effective antibacterial and antimycotic action was obtained upon a variety of microorganisms. Infections were prevented when applied to lacerations and abrasions in emergency treatment as well as in pre- and post-operative applications. Symptomatic relief of pain, itching and dryness was also obtained when the compound was used in the form of a mouth wash.

Of the 5,900 patients treated, only two showed side reactions in the form of a dermatitis. This was cleared with supportive therapy within a week. No evidence of systemic toxicity or iodism was observed.

A Possible Mechanism of the Development of Tolerance to Narcotic Drugs. Axelrod, J. *Science 124*:263 (1956). Studies had shown a striking similarity between the receptors for narcotic drugs and the enzymes that N-demethylate these drugs. The receptors and enzymes were found to be alike with respect to substrates with which they interact, stereospecificity, and antagonism by N-allylnormorphine. Studies were thus undertaken to see if any changes occurring in enzyme activity during the development of tolerance might reflect changes taking place on the drug receptors.

Twelve rats were made tolerant to morphine by daily intraperitoneal injections of 20 mg./Kg. of morphine sulfate. The dose was gradually increased until 150 mg./Kg. was being given. In another group of rats, N-allylnormorphine was given along with morphine. In a third group, the morphine was given as in the first group but then abruptly withdrawn after 35 days. A fourth group acted as a control. Twenty-four hours after the test period, the animals were sacrificed and their livers tested for their ability to N-demethylate morphine, Dilaudid, meperidine, and cocaine.

These tests showed a profound reduction in the ability to N-demethylate morphine by the livers of the morphine-treated animals, an almost identical reduction in ability by the livers of these animals to N-demethylate Dilaudid, a partial reduction in ability to N-demethylate meperidine, and no reduction in ability to N-demethylate cocaine. There was less reduction of this effect in the livers of the rats given both morphine and N-allynormorphine. In the livers of the rats which had had morphine withdrawn, there was no reduction in enzymatic ability.

From the results of this study a striking parallelism between the enzymatic N-demethylation of narcotic drugs and the development of tolerance to the drugs was found. The author concluded that the continuous interaction of narcotic drugs with the demethylating enzymes inactivates the enzymes. He suggested that a similar effect may occur with the receptors of narcotic drugs, resulting in an unavailability of receptor sites with a decreased response to the narcotic drugs.

BOOK REVIEW

Textbooks of Organic Medicinal and Pharmaceutical Chemistry. Third Edition. By Charles O. Wilson and Ole Gisvold. xvi + 823 pages including index. J. B. Lippincott Co., Philadelphia, Pa., 1956. $11.00.

This, the third edition of Organic Medicinal and Pharmaceutical Chemistry, follows the second by only two years; the first, known under the title "Organic Chemistry in Pharmacy", appeared in 1949.

The same group of well-known pharmaceutical chemists participated as collaborators in preparing this new edition as in the previous one and, as before, each chapter is well thought out and clearly written.

The arrangement of the text is based partly on a chemical classification and partly on a pharmacologic, the authors having faced the same practical difficulties as others preparing pharmaceutical texts. Such an arrangement is better for students than a uniform one used in some chemical textbooks.

The teacher of pharmaceutical chemistry or the pharmacy and chemistry of medicinals finds this book of great value since descriptive material, pharmacologic data, official nomenclature, synonyms, etc., are included with the basic chemistry of each drug. This is ideal, particularly for the pharmacy student who must learn the properties and nomenclature of drugs as well as their chemical structure.

The treatment given closely related drugs is excellent in that the student can easily compare, let us say, two morphine derivatives or two antihistamines relating action to structure.

Early chapters on solubility and partition coefficients, hydrogen bonding, chelation, steric relationships, and detoxication help the student understand mechanisms of drug action and the fate of drugs in the body.

While the book is intended primarily for undergraduate students, it is not an elementary or superficial treatise in any sense. Its value as a reference equals its value as a text in this reviewer's opinion. It is without question one of the top ten references that constitute the backbone of a modern pharmaceutical library.

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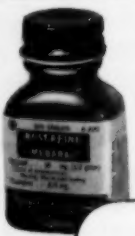

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